Remarks

The specification amendment deletes a duplicate occurrence of the word "of" that occurs on page 6, line 9 of the application as filed.

This Amendment is supplemental to the amendment filed on March 18, 2009 and adds new claims 60-67 presenting further aspects of the invention. The new claims 60-67 recites treatment of a tumor-bearing human subject. Claims 61, 63, 65 and 67 are further limited by a recitation that the non-cyclopamine compound that can be used in place of cyclopamine is a compound that inhibits Hedgehog/Smoothened (Hh/Smo) signaling by binding to the same biological target to which cyclopamine binds to inhibit Hh/Smo signaling.

The present invention is exemplified with descriptions of actual treatments of tumor-bearing human subjects. The specification describes elimination of tumor cells from human subjects by inducing their differentiation and apoptosis with unprecedented selectivity and efficiency achieving decrease of size and disappearance of tumors while sparing the normal cells of patients, including those having stem cell and progenitor cell features. Elimination of tumor cells from a patient while sparing normal cells was considered an unattainable goal in prior art on theoretical grounds as well as in view of the vast clinical experience showing that damaging of normal stem cells and progenitor cells commonly precludes successful treatment (Hannun Y, *Blood* 1997;89:1845-1853). It was further known well that the vast majority of potential drug treatments for cancer found promising in animal models fail in human due to the major differences between human and mouse in tumor structure, genetic stability and physiology and that the differential harming of normal cells in human and mice is a major reason of failure in human (see e.g. the Editorial by Takimoto CH in *Clinical Cancer Research* 2001;7:229-230). Never before in prior art was there a description that cyclopamine or another selective inhibitor of Hh/Smo signaling can be used to cause the presently described and claimed technical effects and therapeutic results, let alone in human. Further, said attainment was highly unexpected and it was even considered impossible in prior art.

The application teaches directly and unambiguously that a molecule other than the cyclopamine used to exemplify the invention can be used to carry out the invention. A non-cyclopamine molecule that can be synthesized or derived from cyclopamine so as to exert the described biological and therapeutic effects of cyclopamine is stated to be suitable to carry out the invention and non-limiting structural features of such a molecule are given (page 10, lines 8-22). The possible structural features that are given are indicated to be non-limiting ("... *may include*") and it is emphasized that a non-cyclopamine molecule that can be used in place of cyclopamine must exert the biological effects of cyclopamine described in the specification (page 10, lines 16-22). Cyclopamine is taught to be an inhibitor of Hh/Smo signaling and references are given describing said well known biological effect of cyclopamine (page 3, lines 2-6). The cited publications Incardona JP et al, *Development* 1998;125:3553-3562 and Cooper MK et al, *Science* 1998;280:1603-1607 had described in prior art that cyclopamine directly and selectively inhibits the Hh/Smo signaling initiated by Shh. See also the incorporated international application PCT/TR01/00027 designating the US (published as WO 02/078703 by WIPO) explicitly teaching that a non-cyclopamine molecule can be used in place of cyclopamine to carry out the described tumor treatment (page 12, lines 1-7). Further, since the tumors to be treated are defined to be those that utilize the Hh/Smo signaling for prevention of apoptosis of tumor cells and for prevention of differentiation of tumor cells (see e.g. PCT/TR01/00027, page 12, lines 1-7; page 6, lines 12-16; present application, page 4, lines 12-17), a person skilled in the art derives a clear unambiguous teaching that a non-cyclopamine molecule that will inhibit Hh/Smo signaling selectively can be used to carry out the invention.

The Smoothened protein, to which cyclopamine binds to inhibit the signaling initiated by a Hh protein in a target cell, was well known in prior art to be obligatory for said signaling (hence the name Hh/Smo signaling in this application). The specification teaches that a non-cyclopamine molecule that exerts the described biological effects of cyclopamine by binding to the same biological target as cyclopamine is suitable to carry out the invention (page 10, lines 16-22). Thus, the claim limitation in the claims 61, 63, 65 and 67 concerning a non-cyclopamine molecule that can be used in place of cyclopamine has support in the application.

The Amendment filed on March 18, 2009 had pointed out to the treatment results showing that causations of presently claimed technical effects and therapeutic results are dependent on the dose of medicament. It is to be noted that a person skilled in the art learns from the originally filed application that a dose of medicament sufficing to consistently inhibit proliferation of tumor cells does not suffice for their elimination by apoptosis. See for example page 14, line 26 to page 15, line 2 and page 6, lines 10-15 where it is described that retraction of basal cell carcinomas (BCCs) from stroma, which is known to be associated with the inhibition of proliferation of BCC cells, was consistently seen in all regions of the tumors excised after application of cyclopamine but not of placebo. As seen from the referred figures, those regions of tumors showing as yet a solid tumor with little or no evidence of apoptosis of the tumor cells nevertheless showed consistent retraction from stroma as a result of exposure to cyclopamine. Numerous post-published investigations confirmed independently that causations of the presently claimed technical effects and therapeutic results require a dose far greater than that sufficing to inhibit proliferation of tumor cells (see e.g. the March 18, 2009 dated Amendment; see further the Hutchin ME et al, *Genes & Development* 2005;19:214-223 publication filed therewith describing that inhibition of tumor cell proliferation *per se* does not suffice to cause their elimination by apoptosis, see e.g. Figures 4d, e showing persistence of the tumor cells rendered nonproliferative). Fundamental reasons also exist that causation of an inhibition of proliferation of tumor cells does not and cannot produce the presently claimed subject matter (see e.g. the June 11, 2007 dated Amendment and the manuscript of Applicant filed therewith).

At least for the reasons given above and articulated with the amendment filed on March 18, 2009, the new claims 60-67 describe subject matter patentable over the prior art.

Respectfully submitted,
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